

References

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Multiple sclerosis and other demyelinating diseases

To the Editor:

Multiple sclerosis has been defined as a chronic progressive disease of the central nervous system, or rather a series of syndromes based on several as-yet-undetermined causative factors.¹ The etiologic factor or factors are unknown, but Harrison² has emphasized its relationship to other demyelinating processes. The pathological change underlying multiple sclerosis is presumed to be demyelination in scattered areas of the brain and spinal cord in plaques of varying size. There is associated edema of the axons and, with progression, degeneration and loss

of function. Vitamins B₁ and B₁₂ are both essential components of myelin.^{4,5} Because demyelination of long nerve axons in the spinal cord is characteristic of severe vitamin B₁₂ deficiency and because this vitamin arrests demyelination in combined system disease, it has been used in the treatment of multiple sclerosis with varying results.^{1-3,6-8}

On the theory that demyelination results from the lack of vitamin B₁ and some factor or factors in liver extract, a therapeutic trial was initiated by the undersigned in 1943. The purpose of this letter is to report the results of that trial.

Materials and methods: Patients were selected on the basis of a history of neurologic deficits suggestive of multiple sclerosis which had been confirmed by neurologic investigation and, in most patients, by a second opinion. The presence of paralysis was felt to be a contraindication to this type of therapy. Fourteen patients were followed up for periods varying from several months to 29 years (Table I).

Routine therapy consisted of in-

Table I
Fourteen patients with multiple sclerosis treated with thiamine hydrochloride and liver extract

Case	Age at onset	Age at 1st treatment	Treatment	Duration of treatment	Current clinical status	Patient's estimate of improvement
1	22	26	Irregular*	1943-1972	Clinically well	95%
2	38 mild 43 severe	43	Irregular	1947-1972	Clinically well	85%
3	26	57	Regular†	1970-1972	Clinically improved	80%
4	25	28	Regular	1971-1972	Clinically well	98%
5	20	41	Regular	1971-1972	Clinically improved	75%
6	26	31	Regular	July-Dec. 1972	Clinically well	95%
7	27	30	Irregular	1971-1972	Improved	50%
8	13 mild 40 severe	49	Regular	1971-1972	Greatly improved	95%
9	37	39	Regular	1971-1972	Improving	50%
10	17	24	Irregular	1964-1972	Improved	80%
11	17	19	Irregular	1962-1964 1967, Mar. 1972	Clinically well	95%
12	48	55	Irregular	1969-1972	Improved	40%
13	35	38	Regular	July-Dec. 1972	Improved	75%
14	26	28	Regular	Jan.-Feb. 1973	Improved	50%

*Irregular: patient receives regular treatment for a period and then does not return for supervision, generally because he or she feels well.

†Regular: patient cooperates in returning for routine therapy.

Sinequan^{*}

25 mg tid

The tranquilizer that is an antidepressant.

The antidepressant that is a tranquilizer.

Indications—The antidepressant and anxiolytic properties of Sinequan have been found to be of value in the drug treatment of:

1. Psychoneurotic patients with anxiety and/or depressive reactions; Anxiety neurosis associated with somatic disorders; Alcoholic patients with anxiety and/or depression.
2. Psychotic depression, including manic-depressive illness (depressed type) and involutional melancholia.

Clinical Use—Controlled clinical trials have confirmed that Sinequan is an effective psychotropic agent with antidepressant and anxiolytic properties. Sinequan has been found useful in alleviating manifest anxiety in neurotic patients including those with somatic disorders. It has also been found useful in patients with neurotic depression including those with mixed anxiety and depression. Patients with endogenous or psychotic depression including manic-depressive illness (depressed type), and involutional melancholia, have also been reported to respond favorably to Sinequan. As adjunctive medication, it appears to benefit some alcoholic patients with chronic anxiety and depressive reactions.

As with most psychotropic agents, some patients with these conditions who have failed to respond to other appropriate medication, may benefit from treatment with Sinequan. In psychoneurotic patients the following symptoms have responded significantly to doxepin: anxiety, tension, depressed mood, somatic concern, guilt feelings, insomnia, fear, apprehension, and worry. Its anxiolytic effect occurs promptly, while onset of the antidepressant effect is delayed and can usually be expected after 10 days or more of treatment.

Dosage and Administration—An optimum daily dosage of Sinequan depends on the condition which is being treated and the response of the individual. Some patients respond promptly; others may not respond for 2 weeks or longer. An initial dosage of 25 mg, t.i.d. is recommended in most patients. This dosage should be increased as required by 25 mg. increments at appropriate intervals until a therapeutic response is obtained. The usual optimum dosage range is 100-150 mg. per day. In some patients, up to 300 mg. per day may be required, but there is rarely any benefit to be obtained by increasing this dosage. In elderly patients it is advisable to proceed more cautiously with dosage increments and to initiate treatment with a lower dosage.

Once a satisfactory therapeutic response has been obtained, it is generally possible to reduce the dosage and still maintain this effect.

Contraindications—Sinequan is contraindicated in individuals who have shown hypersensitivity to the drug.

It is not recommended for children under 12 years of age, since sufficient data on its use in this age group is not yet available.

Because of its anticholinergic activity Sinequan should not be administered to patients with glaucoma or a tendency to urinary retention.

Tricyclic agents are generally contraindicated in patients with a history of blood dyscrasias and severe liver disease.

Sinequan should not be administered concomitantly with MAO inhibitors, since such a combination may cause a syndrome of intensive sympathetic stimulation. Drugs of this type should be discontinued at least two weeks before instituting therapy with Sinequan.

Precautions and Warnings—Although animal reproductive studies have not resulted in any teratogenic effect, the safety of use of Sinequan in pregnancy has not been established and therefore it should be used in pregnant women only when, in the judgment of the physician, it is essential for the welfare of the patients.

Since drowsiness may occur with the use of this drug, patients should be warned of the possibility of this occurring early in the course of treatment, and cautioned against driving a car or operating machinery. Combined use with other drugs acting on the central nervous system should be undertaken with due recognition of the possibility of potentiation. The response to alcohol may also be modified.

As with other antidepressant agents, the possibility of activation of psychotic symptoms should be borne in mind.

Appropriate supervision is required when treating depressed patients, and alternate forms of management should be considered in treating severely depressed patients because of the inherent suicidal risk.

Tricyclic agents may lower the convulsive threshold and should therefore be used with caution in patients with convulsive disorders. Sinequan should be used with caution in patients with cardiovascular disorders. At doses of 300 mg./day or above, it may block the anti-hypertensive effect of guanethidine and related compounds.

Adverse Reactions—Sinequan is generally well tolerated. The following adverse reactions have been reported.

Behavioral Effects: agitation, restlessness, excitement, activation of psychotic symptoms and toxic confusional state.

Anticholinergic Effects: dry mouth, blurred vision, constipation, and genitourinary disorders.

Central Nervous System Effects: drowsiness, insomnia, extrapyramidal symptoms.

Cardiovascular Effects: dizziness, hypotension, tachycardia.

Miscellaneous: fatigue, weight gain, increased sweating and other secretory effects, nausea, heartburn, rash and pruritus, paresthesia, edema, flushing, chills, tinnitus, photophobia, decreased libido.

Supply—Sinequan is available as hard gelatin capsules containing doxepin hydrochloride equivalent to 10, 25 and 50 mg. of doxepin in bottles of 100 and 500.

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travenous thiamine hydrochloride, 150 mg., plus intramuscular injections of liver extract*, 20 µg. (1 ml.), every seven to 10 days for a series of 10 treatments. The patient was then re-evaluated neurologically. Further treatment was recommended depending on the status of the neurologic deficit and the response.

Results and conclusions: The results in the treated patients are summarized in Table I. No patient had progression of the disease while on treatment. When symptoms recurred on cessation of treatment, they were controlled by resumption of therapy.

When vitamins B₁ and B₁₂ were given simultaneously to one patient (case 1) on two occasions (owing to sensitization to liver extract) the patient experienced progression of her deficit. When liver extract and vitamin B₁ therapy was resumed (following desensitization) she improved.

A trial of thiamine hydrochloride, 100 mg. daily by mouth, with regular liver extract therapy (case 4) led to return of symptoms. When routine therapy was again resumed all symptoms cleared. It would appear that some persons may not absorb vitamin B₁ through the gastrointestinal tract.

Patients treated in the early stages of the disease responded well and within a time span appropriate to the presumed underlying pathology of demyelination. Patients in whom the disease was more advanced responded more slowly. Early treatment of the disease or its recurrent symptoms seemed to be more important than the age of the patient. For example, one patient (case 1), now aged 55, still returns for treatment when she considers it necessary because of a lowered sense of well-being, increased fatigue, and a tingling sensation in her hands and feet. Thirty-three years after the onset of her illness and after bed confinement for two years, she is active, does her housework, walks out alone without a cane and enjoys an active social life.

The exact stage of pathological

*Therapy was begun with Lederle's liver extract, but production ceased in the spring of 1972. Connaught Laboratory liver extract was used for a period of nine months. Lilly's liver extract is now used.

change in any patient cannot be determined.⁷ It is logical to assume, however, that the axis cylinders had not been destroyed in any of the patients in this study, even in case 3, a 59-year-old man who refused to accept active therapy until his disease, after many years, had induced almost total incapacity, including poor writing ability and spastic and ataxic gait with dragging of the left foot. His clinical improvement continues and we must assume that remyelination is taking place. At present, this man uses a cane only on the street, can step up with either foot and even uses a ladder. His manual dexterity is good and he writes well.

My experience, like that of Evers,⁹ suggests that early treatment is important in producing symptomatic relief and a state of well-being. In case 2, the patient was treated within six months of the onset of severe symptoms at age 43, made a rapid recovery and gave birth to a normal child two years later. On several occasions, because of irregular therapy, her symptoms recurred, but when treatment was resumed she improved rapidly. Now, at the age of 69, she is active and able to do her housework. In case 4, treatment was instituted within three years of the onset of the disease. The patient cooperated completely and therapy was continued without interruption. After nine months he stated that he felt perfectly well.

The effects of cessation and resumption of therapy are most clearly demonstrated in case 11. Following initial treatment from 1962 to 1964, her condition was improved and treatment was discontinued. In 1967, because of recurrence of symptoms, therapy was resumed on an irregular basis with subsequent improvement. In February 1971 the patient returned with symptoms of fatigue, inability to work, loss of balance and staggering gait. She was not able to return for therapy until March 1972, at which time her neurologic condition had worsened. She had visual and auditory difficulty, scanning speech and poor writing ability, unsteady gait and poor sense of balance. Routine therapy was recommenced and by June 20 of the same year she was able to return to work

as a typist and stated that she felt perfectly well.

The protracted and capricious natural history of multiple sclerosis precludes dogmatic statements regarding the effect of a new therapeutic modality. Furthermore, the exact diagnostic criteria of multiple sclerosis are uncertain, leading to a frequent diagnosis by exclusion appropriate to the uncertainty regarding etiology and pathogenesis. However, with regard to the therapy presented here, patients with two other types of demyelinating diseases have been successfully treated. One of these, a patient with advanced bulbar palsy, is now almost completely asymptomatic. The other, a patient with subacute combined sclerosis who was totally incapacitated, became neurologically entirely negative. My experience suggests that some factor or factors in liver extract, associated with vitamin B₁, can induce remyelination in patients suffering from multiple sclerosis and probably in other cases of demyelinating diseases. It is suggested that this clinical finding should now be subjected to detailed laboratory studies in order to enlarge its use or to circumscribe its limitations.

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